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Online Effects of Beta-tACS Over the Left Prefrontal Cortex on Phonological Decisions

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Abstract—The left posterior inferior frontal gyrus in the prefrontal cortex is a key region for phonological aspects of language processing. A previous study has shown that alpha-tACS over the prefrontal cortex applied before task processing facilitated phonological decision-making and increased task-related theta power. However, it is unclear how alpha-tACS affects phonological processing when applied directly during the task. Moreover, the frequency specificity of this effect is also unclear since the majority of neurostimulation studies tested a single frequency only. The present study addressed the question whether and how 10 Hz online tACS affects phonological decisions. To this end, 24 healthy participants received tACS at 10 Hz or 16.18 Hz (control frequency) or sham stimulation over the left prefrontal cortex during task processing in three sessions. As an unexpected finding, 16.18 Hz significantly impaired task accuracy relative to sham stimulation, without affecting response speed. There was no significant difference in phonological task performance between 10 Hz and 16.18 Hz tACS or between 10 Hz and sham stimulation. Our results support the functional relevance of the left prefrontal cortex for phonological decisions and suggest that online beta-tACS may modulate language comprehension.

Key words: Alpha, beta, prefrontal cortex, plasticity, language, non-invasive brain stimulation.

INTRODUCTION

Language is organized in large-scale networks in the human brain, with a key role of the left prefrontal cortex. A number of previous neuroimaging and neurostimulation studies demonstrated a functional specialization for different aspects of language comprehension within the left prefrontal cortex, with the posterior inferior frontal gyrus being strongly associated with decisions on the sound of words (i.e., phonological decisions) (Poldrack et al., 1999; Gough et al., 2005; Romero et al., 2006; Hartwigsen et al., 2010b; Klaus and Hartwigsen, 2019). The majority of previous neurostimulation studies used short bursts of online repetitive transcranial magnetic stimulation (rTMS) at a frequency of 10 Hz to induce focal perturbations in the left inferior frontal gyrus during phonological tasks at the word level. These studies reported delayed response latencies or increased error rates for effective rTMS relative to sham stimulation or stimulation of a control site. However, the frequency specificity of the disruptive neurostimulation effect is less well explored, although frequency specificity is an important issue that can substantially affect the conclusions from neurostimulation studies (Bergmann and Hartwigsen, 2020).

More recently, a number of studies started to explore the effects of rhythmic stimulation on speech and language processing with transcranial alternating current stimulation (tACS) (see Zoefel and Davis, 2017 for review). Compared to TMS, tACS is a subthreshold stimulation technique that does not evoke action potentials and has the advantage of being cheap, easy to apply and less prone to severe side effects than TMS (e.g. Sandrini et al., 2011). tACS relies on the direct application of alternating electric currents to the scalp with sinusoidal waveforms. The currents travel through the skull and mainly target cortical neurons (for recent reviews, see Elyamany et al., 2021; Vosskuhl et al., 2018). Although the exact mechanisms by which tACS modulates brain activity are still not fully understood, five common explanations for direct, modulatory ''online'' effects include stochastic resonance and rhythm resonance, temporal biasing of spikes, network entrainment and imposed patterns (Liu et al., 2018). These mechanisms are assumed to affect activity in larger networks in the brain. In particu-

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Abbreviations: rTMS, repetitive transcranial magnetic stimulation; tACS, transcranial alternating current stimulation; LME, linear mixed effects; NAS, numerical analogue scale.

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lar, *stochastic resonance* refers to the probability of neurons being either polarized or depolarized by external stimulation depending on their current activity state (see also Miniussi et al., 2013). *Rhythm resonance* is assumed to occur when the tACS frequency is similar to that of the ongoing endogenous oscillations in the stimulated region. *Temporal biasing of spikes* refers to the phenomenon that the spike timing of neurons is regulated by the interaction between the stimulation and internal currents. *Network entrainment* implies that the rhythmic activity of two systems is synchronized, with the internal oscillation synchronizing to the external force. The greater the difference between the internal and the external frequency, the stronger the required force by an external rhythm to entrain an internal oscillation (Herrmann et al., 2016; Thut et al., 2017). Finally, *imposing an arbitrary pattern* on a neuronal network via electrical stimulation requires the strongest field to overcome the endogenous control of network neurons (Liu et al., 2018).

In contrast to these proposed direct online mechanisms of electrical stimulation, the after-effects of tACS likely depend on the induction of neural plasticity (Vosskuhl et al., 2018). In a previous study, we combined offline transcranial alternating current stimulation (tACS) over the bilateral prefrontal cortex with a phonological decision task and electroencephalography to probe the neurophysiological after-effects of 10 Hz tACS in the language system (Moliadze et al., 2019). In that study, we were particularly interested in determining whether 10 Hz tACS can affect behavior in a phonological decision task and how a potential modulation would be reflected in the underlying oscillatory dynamics at rest and during task processing. We expected that 10 Hz tACS should result in behavioral disruption which might be mediated via modulation in the alpha power during task processing. In that study, 10 Hz tACS induced an unexpected facilitatory after-effect on phonological response speed. At the neurophysiological level, there was no significant modulation of activity at rest and no changes in task-related alpha power. However, we found a significant increase in task-related theta power for 10 Hz relative to sham tACS. The individual increase in theta power was correlated with the behavioral facilitation, indicating that increased theta power might be considered as the neurophysiological correlate of the behavioral facilitation. These effects were task-specific since tACS selectively affected response speed in the phonological task but not in a perceptual control task. However, frequency specificity could not be demonstrated since the effects of 10 Hz tACS did not significantly differ from a control frequency in the beta range. These results support the functional relevance of the prefrontal cortex for phonological processing and demonstrate the impact of alpha-tACS on language performance. Yet, the previous study does not provide insight into the immediate online effects of alpha-tACS, which may substantially differ from the plastic after-effects of the stimulation observed in that study (see Bergmann and Hartwigsen, 2020; Vosskuhl et al., 2018). The present study was designed to address this issue. A better understanding of the immediate effects of tACS applied during task processing is mandatory to identify efficient stimulation protocols. One question of interest is whether the behavioral effects of online stimulation (i.e., disruption or facilitation of task performance) are similar for tACS and TMS. Moreover, exploring differences between offline and online effects on task processing helps to understand the potential mechanisms of both approaches, that is, short-term plasticity versus direct modulation of task activity via induction of noise.

To study the immediate consequences of online stimulation, we used an optimized montage with tACS over the left prefrontal cortex being applied via round electrodes. With respect to the expected effect of online tACS on task performance, it should be noted that we are not aware of any similar study investigating phonological processing with alpha-tACS during a task. As noted above, the majority of previous TMS studies showed delayed response speed or decreased task accuracy when 10 Hz rTMS was applied over the prefrontal cortex during phonological or semantic tasks (e.g. Devlin et al., 2003; Gough et al., 2005; Hartwigsen et al., 2010b, 2016; Nixon et al., 2004). Yet, one study also reported facilitation of phonological processing with the same protocol (Klaus and Hartwigsen, 2019), which converges with our previous offline tACS study that found faster phonological response speed after 10 Hz stimulation (Moliadze et al., 2019). Indeed, the direction of behavioral neurostimulation effects may be hard to predict (Sliwinska et al., 2017), and seems to crucially depend, among other factors, on the current brain state (Silvanto et al., 2008; Silvanto and Cattaneo, 2017). Importantly, causality between a stimulated area and its involvement in a specific task is usually assumed whenever a significant effect occurs, irrespective of whether it is facilitatory or inhibitory in nature (Sandrini et al., 2011). Based on these assumptions, we expected that 10 Hz tACS applied during task processing (relative to sham tACS and beta-tACS) should either impair phonological decisions by interfering with ongoing task activity, or facilitate processing if the stimulation would be synchronized with the ongoing task activity (Miniussi et al., 2013). Since online tACS can induce strong artefacts in the EEG signal, we refrained from combining our stimulation protocol with EEG in the present study and focused on the behavioral effects only.

EXPERIMENTAL PROCEDURES

Subjects

Based on our previous study (Moliadze et al., 2019), 24 healthy, native German-speaking students (12 females) aged between 18 and 30 years (M = 23.13, SD = 2.6) participated in the study. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). None of them took any medication or had a history of neurological diseases or other contraindications against stimulation. The study was approved by the local ethics committee of the Medical Faculty at Kiel University, Kiel, Germany (D 416/17). Participants gave written informed consent according to the Declaration of Helsinki on biomedical research involving human subjects. Subjects were recruited via social media

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and flyers at Kiel University. They received one cinema voucher for each session.

Experimental design

Fig. 1 provides an overview of our study which followed a double-blinded randomized cross-over design. Participants underwent three tACS sessions with two stimulation frequencies. During each session, 1 mA tACS was applied over the left prefrontal cortex during a phonological task. The order of stimulation frequencies was counterbalanced across subjects. An inter-session interval of 10 days prevented carry-over effects and minimized learning effects. At the beginning of each session, participants performed a two-minute training of the task. Thereafter, tACS electrodes were mounted. Subjects were placed in front of a 22″ screen (16:9 aspect ratio) at a distance of 60 cm.

In the first 5 min of the stimulation period, participants were asked to sit still with eyes open. Afterwards, a visual cue started the experimental task. Task and stimulation ended simultaneously. Thereafter, the stimulation cap was removed, and participants completed a questionnaire on potential side effects of tACS (adapted from Poreisz et al., 2007). Participants were also asked if they believed that they had received effective or sham stimulation at the end of each session.

Task

We used the same phonological decision task as in our previous studies on phonological processing (Hartwigsen et al., 2010a, 2010b; Moliadze et al., 2019). 300 high-frequency German nouns (150 two- and three-syllable words each, matched for frequency, word length and imageability) were presented in random order and subjects were asked to decide via button press during each trial whether the respective word consisted of two or three syllables. Stimuli were presented for 800 ms and responses were counted from stimulus onset. After stimulus offset, a smoothed fixation point was shown for 1166 ± 166 ms, resulting in an average inter-trial interval of 3000 ms (Fig. 1B). Stimulus presentation and response collection was obtained using PsychoPy 1.8.5.1 (Peirce, 2007).

Stimulation techniques

tACS was applied through a pair of circular saline-soaked surface sponge electrodes (5 × 5 cm). The round sponges were prepared in a standardized procedure. They were stored in a 0.9% NaCl solution before use. Electrodes were inserted in the wet (not saturated) sponge pads. All materials required for stimulation were obtained from Neuroelectrics (Barcelona, Spain).

Electrodes were placed into holes of a neoprene cap corresponding to the international 10/10 EEG system, with the central Cz position aligned to the vertex of the

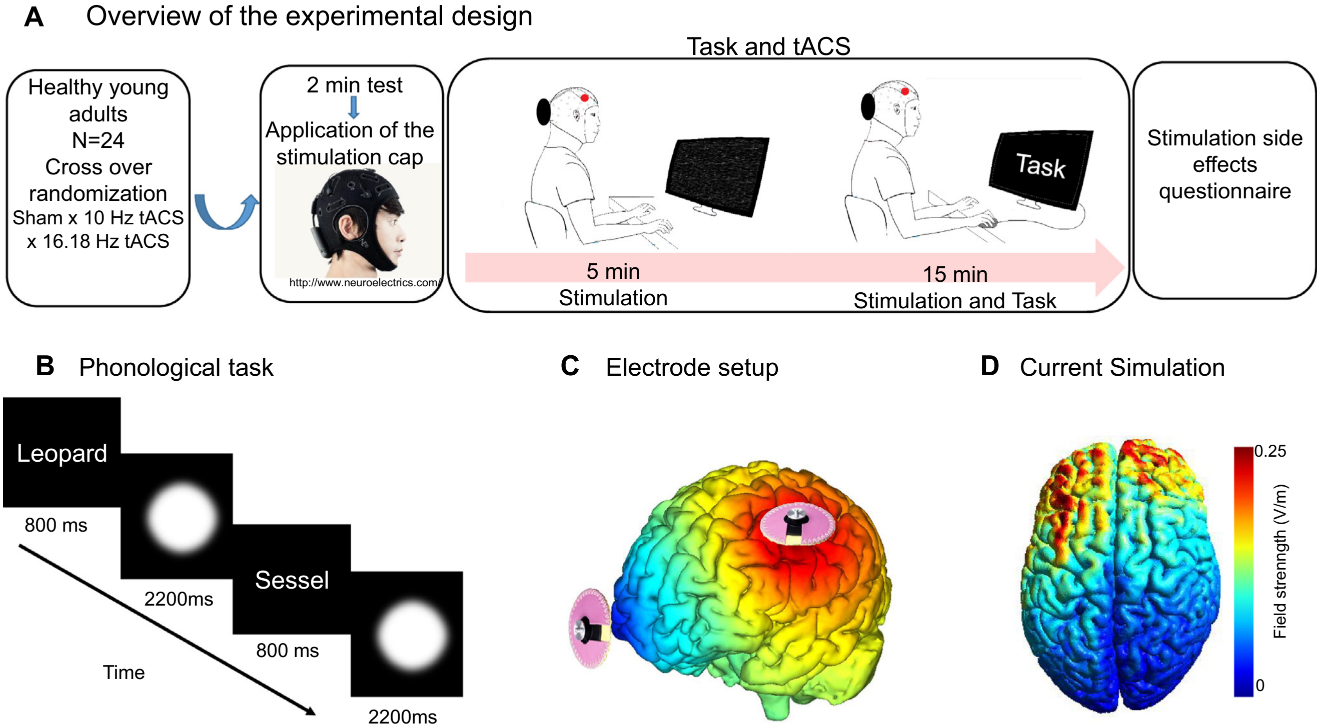

Fig. 1. Experimental design. **(A)** Time-course of the experiment. At the beginning of each session, participants performed a short training of the phonological task. In the first 5 min of the stimulation period, participants were asked to sit still with eyes open. Afterwards, a visual cue started the experimental task. Task and stimulation ended simultaneously. **(B)** Phonological decision task. Stimuli were presented visually for 800 ms and subjects had to decide via button press whether they consisted of two or three syllables. **(C)** Electrode setup. tACS was applied via two round rubber electrodes (25 cm^2). The left prefrontal cortex was located based on the crossing-point of T3-Fz × F7-Cz. The other electrode was placed over Fp2. Visualization is based on NIC software. **(D)** Simulation of the electric field of the stimulation (performed with SimNIBS software).

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Table 1. Behavioral results

Phonological Task Performance (mean± SEM)

	sham tACS	**10 Hz tACS**	**16.18 tACS**
Inverse response time [1/s]	1.46 ± 0.048	1.45 ± 0.045	1.46 ± 0.056
Errors	21.9 ± 2.47	24.4 ± 3.04	26.3 ± 3.17

Post-hoc comparisons for Errors

Stimulation Conditions	**estimate**	**SE**	**z**	***p***
sham tACS-16.18 Hz tACS	-0.161	0.0617	-2.61	**0.0246**
sham tACS-10 Hz tACS	-0.112	0.0623	-1.80	0.17
16.18 Hz tACS-10 Hz tACS	0.049	0.0597	0.821	0.69
Sessions				
S1- S2	0.185	0.0588	3.14	**0.00476**
S1- S3	0.337	0.0612	5.50	**< 0.001**
S2- S3	0.152	0.0637	2.38	**0.045**

Correlations between side effects and behavioral data

Spearman	Pain	Tingling	Itching	Burning	Fatigue	Nervousness	Concentration	Eye Flickering	Vision Problems	Headache	Inconvenience	Sham vs Verum
Errors	**-0.32**	0.06	-0.08	**-0.35**	0.25	0.08	0.21	0.17	0.01	0.07	-0.28	0.1
Response Time	0.22	**0.33**	0.25	0.28	-0.00	0.12	0.05	0.12	-0.16	-0.05	0.02	-0.03

S1-S3= Session 1-3. Bold values indicate statistical significance

head. Current was delivered through each electrode via a wireless Starstim 8 channel neurostimulator. The active electrode was placed over the left prefrontal cortex, based on the crossing-point of T3-Fz × F7-Cz. The "return" electrode was placed over Fp2 (Fig. 1C). Impedances were kept below 10 kΩ. We applied oscillating currents at 10 Hz (frequency of interest), 16.18 Hz (control frequency) or sham stimulation for 20 min with an intensity of 1 mA. The current was ramped up and down over the first and last 8 s of stimulation. During sham stimulation, the current was ramped up for 8 seconds, followed by 30 seconds sham ramp of 1 mA stimulation. As in our previous study, we chose 16.18 Hz as control frequency since the ratio of 16.18 Hz and 10 Hz minimizes the probability of synchronization. The control frequency, considered as frequency of no interest, was defined as 10*1.618 stimulation in the sense of the "golden mean of frequencies", where random cross-frequency synchronization events are assumed to be least frequent (Pletzer et al., 2010), and the sensations of tACS in the beta range are similar to those of tACS in the alpha range (compared to tACS in the theta or gamma range) (Kanai et al., 2008).

Analysis and statistics

Statistical analyses were performed in R 4.0 RC, 2016 (URL https://www.R-project.org/.) The effects of *tACS* (10 Hz, 16.18 Hz or sham) and *session order* (first, second or third) were analyzed with linear mixed effects models (LME) including fixed slopes and random intercept. Degrees of freedom analogous to repeated-measures ANOVAs were approximated using the Kenward-Rogers method (Kenward and Roger, 1997). Prior to analysis, response time data was inversely transformed to avoid potential problems associated with skewed data (Dixon, 2008) and response times for invalid trials were removed. For the error analysis, hierarchical LME models with a Poisson distributed error were fitted to the data and compared with likelihood ratio tests. Using the absolute error count (which, due to the constant trial count is equivalent to the error rate) enabled us to adequately compare errors with common analysis models (Coxe et al., 2009).

For the analysis of the post-hoc questionnaire, the incidence of each side effect was coded in a binary system. The severity of each side effect was rated on a numerical analogue scale (NAS) from one to five; one being very mild and five being an extremely high intensity. The total number of side effects was compared between stimulation conditions with Mann-Whitney tests, intensity was compared using Wilcoxon signed-rank tests.

RESULTS

In the error rate analysis, both *session order* ($\chi^2(2) = 30.8$, $p < 0.001$) and main effect of *tACS* ($\chi^2(2) = 7.07$, $p = 0.029$) were significant, but there was no interaction of *tACS* and *session order* ($\chi^2(4) = 5.47$, $p = 0.243$; (Table 1). The stimulation effect was driven by an increase in the mean error rates for 16.18 Hz relative to sham tACS ($z = -0.161$; $p = 0.0246$) across all sessions (Fig. 2A). The differences between 16.18 Hz and 10 Hz or 10 Hz and sham tACS were not significant (all $p > 0.05$; Table 1). Analysis of response speed showed no significant main effects of *tACS* ($F(2, 40) = 0.09$, $p = 0.918$) and *session order* ($F(2, 40) = 2.48$, $p = 0.097$) and no significant interaction ($F(4, 42.3) = 0.71$, $p = 0.591$) on response speed values (Fig. 2B).

The results of the tACS questionnaire revealed significantly stronger perceived eye flickering effects during both verum stimulations relative to sham tACS (Table 2 for details). All subjects reported about this side effect when they received 16.18 Hz stimulation. Additionally, the perceived mean intensity of the 16.18 Hz stimulation was higher in comparison to the other conditions. None of the other effects reached significance. Although not significant, sham and verum conditions also differed regarding tingling. Overall, less people felt tingling during sham, but those who did so sensed it more intensely. Concerning fatigue, more participants claimed to feel tired during the sham condition relative to both other conditions, although the intensity was slightly higher in the 10 Hz condition. Furthermore, the same amount of people had difficulties with concentrating in all conditions, most intensely during sham. Most participants were able to correctly identify the verum stimulations.

Importantly, we did not find significant positive correlations between tACS-induced changes in behavioral accuracy and side effects (Fig. 2C and Table 2 for details). To the contrary, some correlations were even negative.

DISCUSSION

Here, we combined 10 Hz online tACS over the left prefrontal cortex with a phonological word decision task to investigate modulatory tACS effects on language performance. As an unexpected result, we observed significantly decreased task accuracy during stimulation in the control frequency (16.18 Hz) but not during alpha-tACS. However, this difference was only significant relative to sham stimulation but not between both

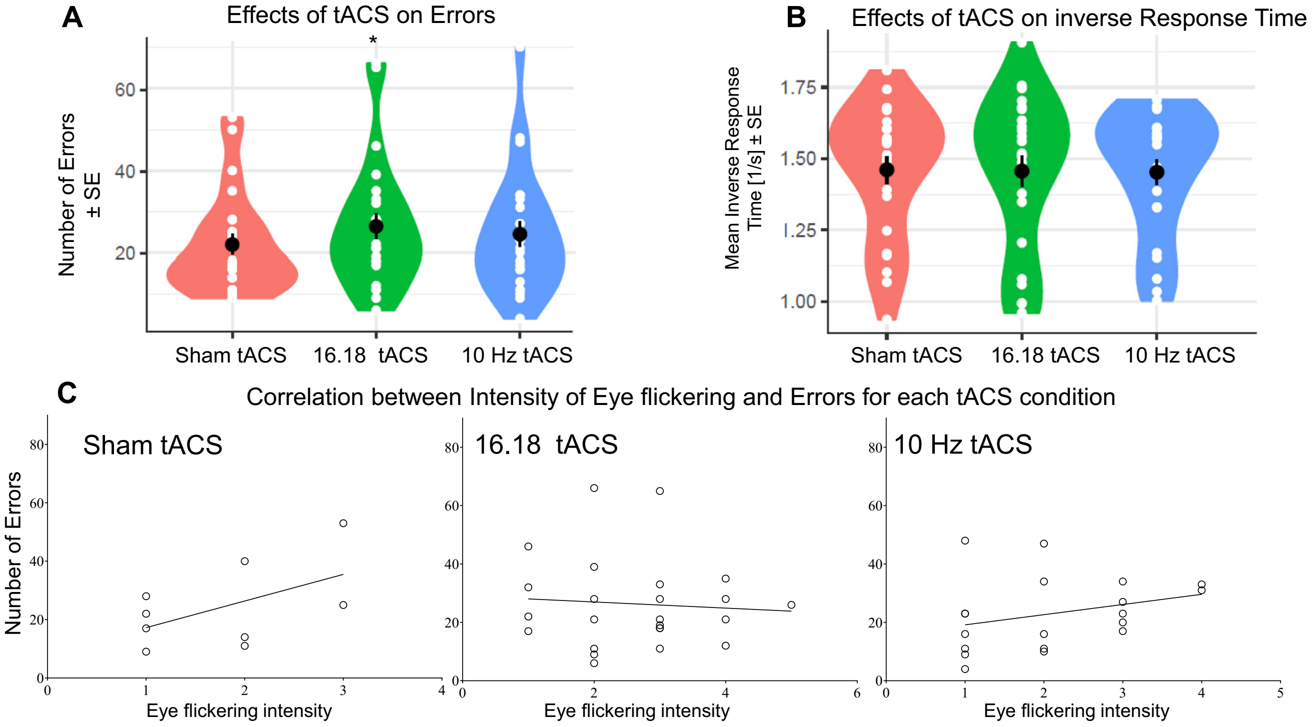

Fig. 2. Behavioral data. **(A)** Effects of tACS on error rates and **(B)** response speed. 16.18 Hz tACS significantly increased error rates relative to sham tACS. **(C)** There was no significant correlation between the number of errors and intensity of eye flickering. White circles represent the individual data points. Violin plots show the distribution across subjects. *$p < 0.05$. Since response times were inversely transformed [1/s], higher values indicate faster responses.

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Table 2. Side effects of transcranial alternating current stimulation

		Sham tACS	10 Hz tACS	16.18 Hz tACS
Light flash	Incidence (beginning)	5 (20%)	10 (42%)	11 (46%)
	Incidence (end)	1 (4%)	3 (13%)	6 (25%)
Electric shock	Incidence (beginning)	4 (17%)	3 (13%)	6 (25%)
	Incidence (end)	3 (13%)	1 (4%)	1 (4%)
Pain	Incidence	2 (8%)	3 (13%)	5 (21%)
	Intensity	1.5 ± 0.7	1	1.8 ± 1.3
Tingling	Incidence	10 (42%)	16 (67%)	16 (67%)
	Intensity	1.9 ± 1.1	1.88 ± 0.81	1.56 ± 1.03
Itching	Incidence	6 (25%)	7 (29%)	7 (29%)
	Intensity	1.7 ± 1.03	1.42 ± 0.53	1.43 ± 0.79
Burning	Incidence	2 (8%)	5 (21%)	4 (17%)
	Intensity	2. ± 1.4	1.4 ± 0.55	1.25 ± 1.5
Fatigue	Incidence	15 (63%)	16 (67%)	15 (63%)
	Intensity	2.27 ± 1.39	2.19 ± 1.05	2.4 ± 1.55
Nervousness	Incidence	3 (13%)	1 (4%)	2 (8%)
	Intensity	1	1	2
Concentration difficulties	Incidence	13 (54%)	14 (58%)	14 (58%)
	Intensity	1.92 ± 1.19	1.71 ± 0.83	2 ± 1.78
Eye flickering	Incidence	9 (38%)	19 (79%)	**24 (100%)**
	Intensity	1.78 ± 0.83	2.11 ± 1.05	2.71 ± 1.12
Vision problems	Incidence	1 (4%)	1 (4%)	4 (17%)
	Intensity	1	1	1.5 ± 0.58
Headache	Incidence	0	4 (17%)	4 (17%)
	Intensity	–	1	1.75 ± 0.96
Inconvenience	Incidence	3 (13%)	4 (17%)	8 (33%)
	Intensity	1.67 ± 1.16	1.25 ± 0.5	1.63 ± 0.74
was verum?		7 (29%)	**18 (75%)**	**24 (100%)**
was sham?		17	6	0

Bold values indicate statistical significance in comparison to sham.

effective conditions. These results contrast with our previous tACS study (Moliadze et al., 2019), which showed faster response speed after 10 Hz tACS but not after 16.18 Hz tACS. The difference is likely explained by the different timing of the stimulation relative to the task. In the previous study, tACS may have primed activity in the stimulated area to a level that was optimal for task processing (Silvanto and Cattaneo, 2017). In contrast, the present study investigated the immediate consequences of ongoing stimulation during task performance. It is plausible that online tACS may have decreased task performance by interfering with task-relevant oscillatory activity in the prefrontal cortex.

Aside from the timing of the stimulation, differences in the behavioral tACS effects between our previous study (Moliadze et al., 2019) and the present findings might also be influenced by the specific electrode montage. In the previous study, we used a bilateral montage, that is, stimulation of both prefrontal cortices (anti-phasic stimulation, i.e., 180° phase difference between the two stimulated sites). Consequently, different patterns were induced by tACS over the left and right prefrontal cortex. In the present study, we chose a "standard" montage with a large electrode over the left prefrontal cortex and the second one over the right supraorbital area, resulting in predominantly left-hemispheric stimulation (see Fig. 1D for a simulation of the current flow).

Notably, electrode size and stimulation intensity are also crucial for the observed outcome. In the current study, we used large electrodes (circular shape with 25 cm^2), resulting in an extended stimulated area under the electrode. With respect to the impact of stimulation intensity, previous studies have demonstrated nonlinear relationships between intensity for transcranial electrical stimulation and outcome even when targeting the primary motor cortex (e.g. Batsikadze et al., 2013; Moliadze et al., 2012; for review see Bergmann and Hartwigsen, 2020). For instance, we have previously reported that high-frequency tACS over the motor cortex led to increased cortical excitability with 1 mA, inhibition of cortical excitability at 0.4 mA and no effect with the intermediate 0.6 and 0.8 mA (Moliadze et al., 2012). It is possible that such effects (increasing stimulation intensities can reverse excitation to inhibition) could also occur in the speech and language domain. In the present study, we chose an intensity of 1 mA since the majority of previous tACS studies in the speech and language domain used intensities around 1 mA (ranging between 0.75 mA and 1.5 mA, see Zoefel and Davis, 2017).

In accordance with our previous findings (Moliadze et al., 2019), we did not observe significant differences between both active conditions in the present study. The absence of frequency-specificity in both studies may indicate that both alpha- and beta-tACS effects on language performance tend to go into the same direction. This explanation seems plausible at least with respect to the observed disruptive online effects in the present study. Indeed, we found a numerical increase in errors for both 16.18 Hz and 10 Hz tACS relative to sham stimulation, but only the former reached significance. Notably, we initially chose 16.18 Hz as control frequency to avoid synchronization between both frequencies (Pletzer et al., 2010) while inducing similar sensations (Kanai et al., 2008). The absolute increase in errors for both protocols may also explain the lack of frequency specificity observed in our study. A potential modulatory effect of both frequencies on language performance would be supported by previous TMS studies in the language domain which reported significant perturbation effects for online rTMS over the prefrontal cortex at both frequencies (10 Hz rTMS: Devlin et al., 2003; Gough et al., 2005; Hartwigsen et al., 2010b; 20 Hz: see Beynel et al., 2019 for a meta-analysis). Given the overall low number of online tACS studies in the language domain in general (see Zoefel and Davis, 2017 for review), and those using online beta-tACS in particular, this hypothesis remains to be tested in future tACS studies. While the underlying neurophysiology of disruptive online effects of both tACS and rTMS is not well understood, it is likely that high-frequency protocols of both techniques may induce noise in the stimulated area that interferes with the ongoing task signal and thereby decreases performance (Miniussi et al., 2013). Importantly, our results emphasize the need for an active control condition to explicitly test frequency specificity, which is usually ignored in the majority of NIBS studies to date (Bergmann and Hartwigsen, 2020). Another important issue which is particularly relevant for online stimulation protocols is related to the side effects of a particular NIBS protocol. In our study, side effects were measured after stimulation with a questionnaire, which is a common approach in NIBS studies (e.g. Poreisz et al., 2007). Could the observed significant increase in errors under beta-tACS simply be explained by the potentially distractive side effects of the stimulation? Importantly, neither of the two effective protocols was significantly different from sham stimulation in terms of the subjective ratings of inconvenience, concentration difficulties, pain, headache or vision problems. However, beta-tACS caused significantly stronger eye flickering sensations and both effective protocols were successfully identified as verum stimulation in the majority of participants (alpha-tACS: 75%, beta-tACS: 100%). This may have influenced the disruptive stimulation effects. Interestingly, we did not observe a significant tACS-induced modulation of response speed in the present study which would have been expected if the disruptive effects were completely explained by distractive side effects. More importantly, the absence of a significant positive correlation between individual eye flickering sensations and number of errors argues against a selective explanation of the tACS-induced disruption in our data in terms of side effects. Notably, some of the correlations between side effects and behavioral stimulation effects were even negative. Consequently, while some side effects may have contributed to increased errors under tACS, they are unlikely to fully explain the observed effects. Future studies may use anaesthetic gel to prevent some of the stimulation-induced side effects (Antal et al., 2017). However, this does not reduce the stimulation-induced flickering sensations. Here, the inclusion of a control task would help to test the specificity of the observed effects. In the present study, we did not include a control task because we did not want to extend the stimulation duration for more than 20 min. Stimulation of 24 min and more has been demonstrated to reverse the effects of a given transcranial electrical stimulation protocol, at least for plasticity-inducing transcranial direct current stimulation (Hassanzahraee et al., 2020). We chose to stimulate 5 min without a task to allow for the unfolding of the modulatory tACS effect before the 15-minute task period was started.

In summary, we provide evidence that beta-tACS applied over the left prefrontal cortex during task processing interferes with phonological decisions. These findings support the role of the left posterior prefrontal cortex in phonological aspects of language comprehension and demonstrate that tACS is an effective tool to modulate higher cognitive functions. Future studies should test whether these effects are task- and frequency-specific or whether similar effects can be obtained with alpha-tACS. Future studies should also explore the underlying neurophysiological effects of online tACS at the level of brain oscillations once effective artefact correction methods are available.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, et al. (2017) Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol 128:1774–1809.

Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA (2013) Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 591:1987–2000.

Bergmann TO, Hartwigsen G (2020) Inferring causality from noninvasive brain stimulation in cognitive neuroscience. J Cogn Neurosci:1–29.

Beynel L, Appelbaum LG, Luber B, Crowell CA, Hilbig SA, Lim W, Nguyen D, Chrapliwy NA, et al. (2019) Effects of online repetitive transcranial magnetic stimulation (rTMS) on cognitive processing: a meta-analysis and recommendations for future studies. Neurosci Biobehav Rev 107:47–58.

Coxe S, West SG, Aiken LS (2009) The analysis of count data: a gentle introduction to poisson regression and its alternatives. J Pers Assess 91:121–136.

Devlin JT, Matthews PM, Rushworth MFS (2003) Semantic processing in the left inferior prefrontal cortex: a combined functional magnetic resonance imaging and transcranial magnetic stimulation study. J Cogn Neurosci 15:71–84.

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Dixon P (2008) Models of accuracy in repeated-measures designs. J Mem Lang 59:447–456.

Elyamany O, Leicht G, Herrmann CS, Mulert C (2021) Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. Eur Arch Psychiatry Clin Neurosci 271:135–156.

Gough PM, Nobre AC, Devlin JT (2005) Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. J Neurosci 25:8010–8016.

Hartwigsen G, Baumgaertner A, Price CJ, Koehnke M, Ulmer S, Siebner HR (2010a). Phonological decisions require both the left and right supramarginal gyri. Proc Natl Acad Sci U S A (107):16494–16499.

Hartwigsen G, Price CJ, Baumgaertner A, Geiss G, Koehnke M, Ulmer S, Siebner HR (2010b). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: Evidence from dual-site TMS. Neuropsychologia (48):3155–3163.

Hartwigsen G, Weigel A, Schuschan P, Siebner HR, Weise D, Classen J, Saur D (2016) Dissociating parieto-frontal networks for phonological and semantic word decisions: a condition-and-perturb TMS study. Cereb Cortex 26:2590–2601.

Hassanzahraee M, Nitsche MA, Zoghi M, Jaberzadeh S (2020) Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: an investigation for induction of counter-regulatory mechanisms. Brain Stimul 13:832–839.

Herrmann CS, Murray MM, Ionta S, Hutt A, Lefebvre J (2016) Shaping intrinsic neural oscillations with periodic stimulation. J Neurosci 36:5328–5337.

Kanai R, Chaieb L, Antal A, Walsh V, Paulus W (2008) Frequency-dependent electrical stimulation of the visual cortex. Curr Biol 18:1839–1843.

Kenward MG, Roger JH (1997) Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 53:983–997.

Klaus J, Hartwigsen G (2019) Dissociating semantic and phonological contributions of the left inferior frontal gyrus to language production. Hum Brain Mapp 40:3279–3287.

Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Yu, Opitz A, Mehta A, et al. (2018) Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun 9:5092.

Miniussi C, Harris JA, Ruzzoli M (2013) Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 37:1702–1712.

Moliadze V, Atalay D, Antal A, Paulus W (2012) Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul 5:505–511.

Moliadze V, Sierau L, Lyzhko E, Stenner T, Werchowski M, Siniatchkin M, Hartwigsen G (2019) After-effects of 10Hz tACS over the prefrontal cortex on phonological word decisions. Brain Stimul 12:1464–1474.

Nixon P, Lazarova J, Hodinott-Hill I, Gough P, Passingham R (2004) The inferior frontal gyrus and phonological processing: an investigation using rTMS. J Cogn Neurosci 16:289–300.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

Peirce JW (2007) PsychoPy–Psychophysics software in Python. J Neurosci Methods 162:8–13.

Pletzer B, Kerschbaum H, Klimesch W (2010) When frequencies never synchronize: the golden mean and the resting EEG. Brain Res 1335:91–102.

Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JDE (1999) Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage 10:15–35.

Poreisz C, Boros K, Antal A, Paulus W (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 72:208–214.

Romero L, Walsh V, Papagno C (2006) The neural correlates of phonological short-term memory: a repetitive transcranial magnetic stimulation study. J Cogn Neurosci 18:1147–1155.

Sandrini M, Umiltà C, Rusconi E (2011) The use of transcranial magnetic stimulation in cognitive neuroscience: a new synthesis of methodological issues. Neurosci Biobehav Rev 35:516–536.

Silvanto J, Cattaneo Z (2017) Common framework for ‘‘virtual lesion” and state-dependent TMS: The facilitatory/suppressive range model of online TMS effects on behavior. Brain Cogn 119:32–38.

Silvanto J, Muggleton N, Walsh V (2008) State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 12:447–454.

Sliwinska MW, Violante IR, Wise RJS, Leech R, Devlin JT, Geranmayeh F, Hampshire A (2017) stimulating multiple-demand cortex enhances vocabulary learning. J Neurosci 37:7606–7618.

Team R, 2016. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Thut G, Bergmann TO, Fröhlich F, Soekadar SR, Brittain J-S, Valero-Cabré A, Sack AT, Miniussi C, et al. (2017) Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. Clin Neurophysiol 128:843–857.

Vosskuhl J, Struber D, Herrmann CS (2018) Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. Front Hum Neurosci 12:211.

Zoefel B, Davis MH (2017) Transcranial electric stimulation for the investigation of speech perception and comprehension. Lang Cogn Neurosci 32:910–923.

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